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A commentary reprinted from the April 8, 2026 issue of Mealey's Litigation Report: Asbestos

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Commentary

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There are numerous cases pending in various courts in the United States in which the claim is that exposure to asbestos through some product caused the plaintiff's or decedent's mesothelioma. Plaintiffs' attorneys and plaintiffs' experts have historically argued that the sole cause of mesothelioma is asbestos exposure and that mesothelioma cannot develop in the absence of asbestos exposure. In direct contrast to those assertions, numerous recent medical studies have been published in peer-reviewed literature that demonstrate mesothelioma can occur in the absence of asbestos exposure and that genetic predisposition alone is causative of mesothelioma. In fact, there have been reports in the literature that approximately 20% of mesothelioma cases may be related to genetic predisposition.[1] As such, when defending mesothelioma cases, defense attorneys should consider if genetics may be a viable causation defense.

Generally speaking, cancer is the accumulation of genetic damage to genes in the cells of our body. Genes are sections of DNA that control the way our cells work. Changes to those genes can cause the cells to malfunction, which can lead to cancer.

As far as how that genetic damage can occur, genetic damage can be inherited. Genetic damage can develop spontaneously. And genetic damage can occur from exposures to environmental factors. Because an individual can both be born with genetic damage that can result in cancer as well as have genetic damage occur during their lifetime that can result in cancer, it is important for attorneys to understand the difference between germline and somatic mutations when assessing a genetics defense.

Germline and somatic mutations differ primarily in where and when they occur in the body. Germline mutations are changes in DNA that individuals are born with. These mutations are often inherited and can play a role in genetic disorders and familial cancers. In contrast, somatic mutations occur in cells during an individual's lifetime, often due to environmental factors, replication errors, or exposure to mutagens. Somatic mutations are not inherited but can lead to cancer.

Often times, the individual diagnosed with mesothelioma may have medical records that discuss the results of somatic testing. The somatic testing is often done using tumor tissue. But when considering if a genetics defense is viable, it is important to analyze if the individual has germline mutations that may have caused the cancer. To assess if a genetics defense is available based on germline mutations, attorneys should consider seeking a court order requiring the individual with mesothelioma to provide a blood or saliva sample for whole genome sequencing.

Whole genome sequencing is a method used to determine the complete DNA sequence of an organism's genome. Unlike targeted sequencing, which focuses on specific genes or regions, whole genome sequenc-

ing captures all genetic information, including germline mutations. This technique involves breaking the DNA into small fragments, sequencing them, and then using computational tools to assemble the sequences into a full genome map. Whole genome sequencing can be used to determine if an individual has specific genetic mutations that may be causative of a cancer.

Some courts may not allow access to the full results of whole genome sequencing and, instead, will limit the reported results to certain mutations in certain genes. But when assessing a genetic defense, as much genetic information as possible should be obtained. So attorneys should seek the full results of the whole genome sequencing. The full results may provide useful information to assess a genetics defense because there continues to be new literature that identifies newly discovered driver mutations for mesothelioma.

As far as the medical literature, there are numerous articles that state genetics can predispose an individual to mesothelioma.[2] The distinction between predisposition and susceptibility to mesothelioma is important when considering a genetics defense. Predisposition refers to an inherited tendency or genetic makeup that increases the likelihood of developing a disease. Susceptibility means being vulnerable or more likely to be affected by a disease due to environmental or lifestyle factors. Plaintiffs' attorneys and experts will argue that genetics alone is not causative of mesothelioma; instead, genetics merely make an individual more susceptible to developing mesothelioma at lower levels of asbestos exposure and at shorter latency periods.

Yet, in direct opposition to plaintiffs' argument, there are numerous articles that state genetically-driven mesotheliomas can develop in the absence of asbestos exposure. In fact, one article from 2025 states:

> This genetic predisposition is a risk factor for mesothelioma that is independent of exposure to asbestos . . . . In other words, this predisposition is an independent risk factor for mesothelioma and does not increase susceptibility to asbestos-related mesotheliomas.[3]

Similarly, another article from 2022 states: "Germline mutation carriers can develop pleural or peritoneal mesotheliomas often with no or minimal asbestos exposure."[4] As such, the literature stands for the proposition that genetic mutations predispose individuals to developing mesothelioma. In fact one article concludes: "One of the great challenging facing the scientific community in the future will be the distinction between cases caused by genetic susceptibility alone and those for which the individual is unusually susceptible to relatively low levels of asbestos exposure."[5]

As far as genetic mutations that predispose individuals to mesothelioma, the most common mutation discussed in the literature is BAP1.[6] Research shows that individuals with BAP1 mutations can develop mesothelioma without asbestos exposure. In a 2025 article, the authors wrote:

> The discovery of BAP1 germline mutations has reshaped our understanding of mesothelioma, traditionally considered almost exclusively as an environmentally driven disease linked to asbestos exposure. Up to now, 20% to 30% of patients with malignant mesothelioma have no context of asbestos exposure. The recognition of a BAP1 tumor predisposition syndrome underscores that mesothelioma can, in some families, arise from inherited genetic susceptibility rather than occupational or environmental exposure alone.[7]

While BAP1 mutations have been the primary focus of genetically-driven mesotheliomas in the literature, the medical literature states that other genes may also play a role in causing mesothelioma.[8] Further, multiple genetic mutations in multiple genes may work together to cause mesothelioma. This is why having the results of whole genome sequencing is helpful when determining if a case has a viable genetics defense.

Further, when assessing if a case may have a genetics defense, there are certain clinical factors that make a genetically-driven mesothelioma more likely. First, there is literature that states that individuals who develop mesothelioma at a younger age are less likely to have asbestos exposure and more likely to have a genetic predisposition.[9] In general, the latency period between exposure to asbestos and development of mesothelioma is 30-50 years.[10] So when an individual

develops mesothelioma at an age young enough to not include a sufficient latency period, the mesothelioma is more likely driven by genetics instead of asbestos exposure.

Second, mesotheliomas that are driven by germline mutations are less aggressive than mesotheliomas caused by asbestos exposure.[11] Because of that, individuals with genetically-driven mesothelioma live for years longer than individuals who have mesotheliomas caused by asbestos exposure.[12] In addition, genetically-driven mesotheliomas respond better to therapy.[13]

Third, asbestos-driven mesotheliomas typically present at a single site. In contrast, genetically-driven mesotheliomas may present at multiple sites, such as multiple body cavities.[14]

Fourth, there are certain markers that may indicate an individual was exposed to asbestos. Specifically, asbestosis, pleural plaques, and asbestos bodies can indicate that an individual was exposed to asbestos.[15] Even so, some of those markers, such as pleural plaques, can be seen even in the absence of asbestos exposures.[16] Regardless, in cases in which all of those markers are absent, those individuals may not have been exposed to asbestos, and genetics alone may be the cause of their mesothelioma.

In summary, the evolving scientific literature supports the position that genetic predisposition—particularly germline mutations such as BAP1—can be a complete and independent cause of mesothelioma. Defense counsel should consider genetic testing and expert analysis as part of a comprehensive causation defense.

Endnotes

1. Maria Teresa Congedo, *The genetic susceptibility in the development of malignant pleural mesothelioma: somatic and germline variants, clinicopathological features and implication in practical medical/surgical care: a narrative review*, 16(1) J. Thorac. Dis. 671, 671 (2024) ("Several candidate genes have been associated with a predisposition to MPM and most of them play a role in DNA repair mechanisms: overall, approximately 20% of MPM cases may be related to genetic predisposition.").
2. Maria Teresa Congedo, *The genetic susceptibility in the development of malignant pleural mesothelioma: somatic and germline variants, clinicopathological features and implication in practical medical/surgical care: a narrative review*, 16(1) J. Thorac. Dis. 671, 671 (2024) ("Several candidate genes have been associated with a predisposition to MPM and most of them play a role in DNA repair mechanisms: overall, approximately 20% of MPM cases may be related to genetic predisposition.").
3. Callan F. Krevanko, *Potential influence of cancer history on mesothelioma incidence: an ecologic analysis in the U.S. population*, 47(4) J. Pub. Health 1, 4 (2025); *see also* Michele Carbone, *Mesothelioma: Scientific Clues for Prevention, Diagnosis, and Therapy*, 69 CA Cancer J. Clin. 402, 406 (2019) ("As the cohorts of asbestos workers vanish because of old age, increasing percentages of mesotheliomas, especially peritoneal mesotheliomas, occur in individuals who are not occupationally exposed to asbestos. These mesotheliomas may be caused by environmental exposure, genetic predisposition, or GxE interaction. . . . Pathogenic germline mutations of BAP1 and, less frequently, of other tumor suppressor genes have been detected in approximately 12% of patients. This subgroup of genetically linked mesotheliomas occur in younger individuals who rarely report asbestos exposure.").
4. Juuso Paaganen, *The Rocky Road from Preclinical Findings to Successful Targeted Therapy in Pleural Mesothelioma*, 23(21) Int. J. Mol. Sci. 1, 2 (2022).
5. Victor L. Roggli, *Chronological trends in the causation of malignant mesothelioma: Fiber burden analysis of 619 cases over four decades*, 230 Environ. Res. 1, 6 (2023).
6. *See generally* Francoise Galateau-Salle, *Mesothelioma in BAP1 Cancer Syndrome and Contribution of Epigenetic*, 20(11) J. Thorac. Onc. 1580 (2025); Michele Carbone, *Mesothelioma: Scientific Clues for Prevention, Diagnosis, and Therapy*, 69 CA Cancer J. Clin. 402, 403 (2019) ("In addition, germline mutations of BRCA1-associated protein (BAP1) and of other tumor suppressor genes have been causally linked to mesothelioma, at times together with exposure to asbestos or other carcinogenic fibers.").
7. Francoise Galateau-Salle, *Mesothelioma in BAP1 Cancer Syndrome and Contribution of Epigenetic*, 20(11) J. Thorac. Onc. 1580, 1580 (2025).

8. Michele Carbone, *Mesothelioma: Scientific Clues for Prevention, Diagnosis, and Therapy*, 69 CA Cancer J. Clin. 402, 409 (2019) ("In addition to BAP1, other tumor suppressor genes have recently been found to cause a hereditary predisposition to mesothelioma—and to other cancers—in several families in the United States and abroad: overall, at least 12% of mesotheliomas occur in carriers of genetic mutations. Most of these heterozygous germline mutations occur in genes that regulate DNA repair, such as MLH1, MLH3, TP53, BRCA2, etc."); Michele Carbone, *Medical and Surgical Care of Patients with Mesothelioma and Their Relatives Carrying Germline BAP1 Mutations*, 17(7) J. Thorac. Oncol. 1, 3 (2022) ("This paper focuses on BAP1; however, the concepts discussed may apply more widely to individuals carrying other pathogenic germline mutations that cause other tumor predisposition syndrome/cancer syndromes, as in these individuals mesothelioma may occasionally develop and may also be associated with prolonged survival."); Flavia Novelli, *Germline BARD1 variants predispose to mesothelioma by impairing DNA repair and calcium signaling*, 121(29) Genetics 1, 1 (2024) ("We also found some mesotheliomas developing in younger patients and associated with prolonged survival that did not contain mutations of any of the genes tested, which included those known to predispose to cancer. We suspected that additional genes, not included in our testing panel might cause or predispose to less aggressive mesotheliomas in younger patients.").

9. Alyssa Kraynie, *Malignant mesothelioma not related to asbestos exposure*, 40(3) Ultrastruct. Pathol. 1, 2-3 (2016) ("The mean age of the asbestos-related group was 66 years (range 31-94), while the mean age of the non-asbestos-related group was 55 years.").

10. Victor L. Roggli, *Chronological trends in the causation of malignant mesothelioma: Fiber burden analysis of 619 cases over four decades*, 230 Environ. Res. 1, 2 (2023) ("In consideration of the 30-40 year lag time from initial exposure to asbestos until the diagnosis of mesothelioma"); Michele Carbone, *Mesothelioma: Scientific Clues for Prevention, Diagnosis, and Therapy*, 69 CA Cancer J. Clin. 402, 403 (2019) ("The latency from asbestos exposure to the development of mesothelioma is about 30 to 50 years.").

11. Michele Carbone, *Medical and Surgical Care of Patients with Mesothelioma and Their Relatives Carrying Germline BAP1 Mutations*, 17(7) J. Thorac. Oncol. 1, 2 (2022) ("Some malignancies in germline BAP1 mutations carriers, mesotheliomas in particular are much less aggressive. . . . This is significantly different than the 6 to 24 month median survival for sporadic—that is, not genetically related—mesothelioma, depending on histology.").

12. Michele Carbone, *Mesothelioma: Scientific Clues for Prevention, Diagnosis, and Therapy*, 69 CA Cancer J. Clin. 402, 415 (2019) ("Patients with mesothelioma who carried germline mutations experienced a significantly prolonged survival of 5 to >10 years, only 28% reported possible asbestos exposure."); Flavia Novelli, *Germline BARD1 variants predispose to mesothelioma by impairing DNA repair and calcium signaling*, 121(29) Genetics 1, 1 (2024) ("We found that BAP1-linked mesotheliomas had a distinct clinical presentation: These patients very rarely had evidence of asbestos exposure, the median age of onset was 54 y old, several of them were in their 20s and 30s, the male to female and the pleural to peritoneal mesothelioma ratios were 1:1, compared to about 7:1 in mesotheliomas developing in asbestos workers. Intriguingly, mesotheliomas developing in carriers of germline BAP1 mutations had a median survival of 5-7 y and some were apparently cured as they survived mesothelioma for > 20 y. In contrast, mesotheliomas developing in asbestos workers have a median survival of ~1 y, are resistant to therapy, and are uniformly fatal. These differences point to different mechanisms underlying the pathogenesis of these malignancies.").

13. Michele Carbone, *Medical and Surgical Care of Patients with Mesothelioma and Their Relatives Carrying Germline BAP1 Mutations*, 17(7) J. Thorac. Oncol. 1, 4 (2022) ("in this particular group of patients, who are usually young, do not have evidence of asbestos exposure, seem to respond to therapy, and often have excellent survival").

14. Xinwei Wu, *Prospective Analysis of Mesothelioma in Subjects With BAP1 Cancer Syndrome: Clinical Characteristics and Epigenetic Correlates of Disease*, J. Thorac. Onc. 1, 14 (2025) ("Although no direct comparison was performed, our prospective findings (including our recent retrospective analysis) strongly suggest that mesotheliomas arising in subjects with germline BAP1 mutations are distinctly

different from sporadic mesotheliomas with or without somatic BAP1 mutations. Whereas sporadic mesotheliomas predominantly involve one body cavity, germline BAP1 mutant mesotheliomas arise as synchronous multicompartment malignancies.").

15. Victor L. Roggli, *Chronological trends in the causation of malignant mesothelioma: Fiber burden analysis of 619 cases over four decades*, 230 Environ. Res. 1, 1 (2023) ("Certain objective markers such as clinical or pathological findings of asbestosis, radiographic or pathologically identified plural plaques, or asbestos bodies in histological sections of lung tissue are useful predictors of an asbestos etiology.").

16. Alyssa Kraynie, *Malignant mesothelioma not related to asbestos exposure*, 40(3) Ultrastruct. Pathol. 1, 3 (2016) ("Pleural plaques were identified in 63% of the asbestos-related cases and in 7% of the non-asbestos-related cases."). ■

MEALEY'S LITIGATION REPORT: ASBESTOS
edited by Bryan Redding
The Report is produced twice monthly by

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Web site: lexisnexis.com/mealeys
ISSN 0742-4647

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